

# Synthetic Laxatives

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A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS  
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE  
UNIVERSITY OF MICHIGAN

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By

O. J. Weinkauff

1931

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EASTON, PA.  
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## TABLE OF CONTENTS

|                                                                                              |    |
|----------------------------------------------------------------------------------------------|----|
| PART I. A New Method for the Preparation of Diarylphthalides .....                           | 5  |
| PART II. The Preparation of 2 - (4'' - Hydroxybenzoyl) - 4' - hydroxybenzo-<br>phenone ..... | 13 |
| PART III. The Preparation of Several Substituted Anthrones .....                             | 19 |



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## PART I

### A NEW METHOD FOR THE PREPARATION OF DIARYLPHTHALIDES

During a study of synthetic laxatives it became necessary to obtain a supply of phenolphthalein (4',4''-dihydroxydiphenylphthalide) entirely free from the by-products which result during the manufacture of this substance. Certain of these by-products—presumably some type of anthraquinone—are extremely potent cathartics and yellow phenolphthalein, that is, phenolphthalein which has not been subjected to a thorough purification process and which is contaminated with a small quantity of a yellow, alkali-soluble, resinous material, is used extensively as a laxative.<sup>1</sup>

Furthermore, we wished to obtain a sample of isophenolphthalein (2',4''-dihydroxydiphenylphthalide) in order that its physiological properties might be reinvestigated. In a preliminary report by Hatcher<sup>2</sup> it is recorded that isophenolphthalein exhibits no cathartic action on humans. In view of the fact that this substance differs from phenolphthalein only in the respect that it is a 2',4''-dihydroxy instead of a 4',4''-dihydroxy derivative, it would be conceivable that the material might be less active than phenolphthalein but it seemed very strange that the compound should have been found to be entirely inert. Although our tests were carried out only on a very limited scale, the results obtained with the isophenolphthalein prepared by us agreed with those of Hatcher. Administered, mixed with milk sugar, in the form of gelatine capsules, no laxative effect was obtained with human subjects even with doses as large as four grains.

One of the objectionable features of many of the syntheses described hitherto is that in addition to the desired phthalide, by-products such as isomeric phthalides or anthraquinone derivatives are usually formed.

It seemed to us that the following method might be a very satisfactory one, not only for the synthesis of phenolphthalein and isophenolphthalein but also for a variety of diarylphthalides, since only one phthalide could be produced and the formation of an anthraquinone would be impossible; moreover, due to the procedure employed, the positions of any substituents in the phthalide molecule would be known with certainty.

Benzophenone should yield the MgBr derivative of 2-methyltriphenyl-

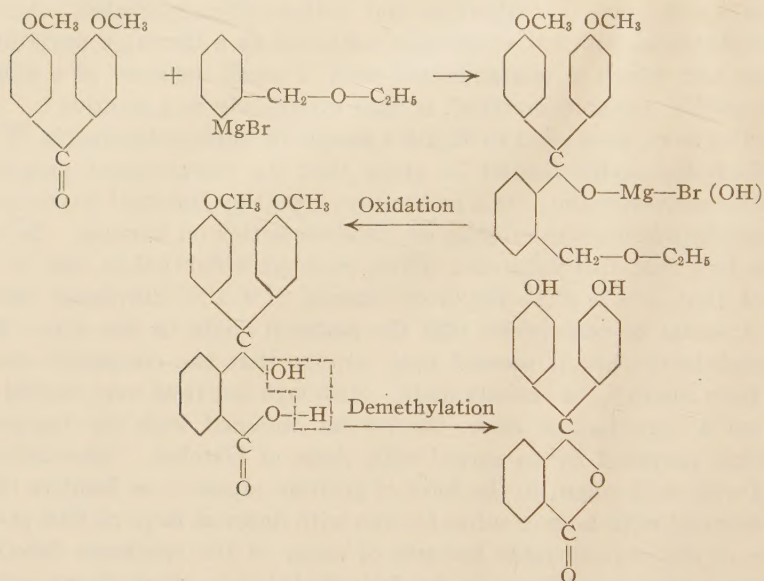
<sup>1</sup> Pasternack, U. S. Patent, 1,681,361 (1928).

<sup>2</sup> Hatcher, see Orndorff and Barrett, *J. Am. Chem. Soc.*, **46**, 2487 (1924).



carbinol when treated with 2-methylphenylmagnesium bromide. Upon hydrolysis of this compound to the carbinol and oxidation of the methyl group to carboxyl, with spontaneous elimination of water from the molecule, diphenylphthalide should be formed. Although we were able by this method to obtain diphenylphthalide from benzophenone, and fluoran from 2,2'-dimethoxybenzophenone, the yields of the phthalides were low due to the difficulty encountered in the oxidation of the methyl group. However, by a slight modification of the above procedure, namely, the use of the Grignard reagent prepared from 2-ethoxymethylphenyl bromide instead of that from 2-methylphenyl bromide, it was found possible to prepare diphenylphthalide, phenolphthalein, isophenolphthalein and fluoran in fairly good yields.

The following series of reactions illustrates the process for the preparation of phenolphthalein<sup>3</sup>



We attempted to prepare isophenolphthalein by the method of Orndorff and Barrett.<sup>4</sup> According to these investigators this product was obtained

<sup>3</sup> We have not been able by the use of the method described above to prepare certain mono- and dihydroxydiarylphthalides although the syntheses of the corresponding tertiary carbinols have been described in the experimental part of the paper; in some cases the compounds seemed to decompose during the oxidation of the side chain, in others during demethylation. The applicability of the procedure for the preparation of a number of other substituted diarylphthalides is under investigation and it has been found, so far, that 3',3''-dibromophenolphthalein can be obtained from 3,3'-dibromo-4,4'-dimethoxybenzophenone.

<sup>4</sup> Orndorff and Barrett, *J. Am. Chem. Soc.*, **46**, 2488 (1924).

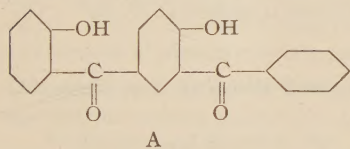


by them in 87% yield from the condensation of 2-(2'-hydroxybenzoyl)-benzoic acid with phenol in the presence of stannic chloride at 100–110°. Although the procedure was repeated a number of times and various condensation agents were used, we were unable to isolate any of the desired product. Instead there was obtained *phenolphthalein* in 40% yield, a small quantity of fluoran and a tar. It is possible, of course, that the latter may have contained some isophenolphthalein. Orndorff and Barrett make no mention of phenolphthalein as a reaction product. The formation of the latter was entirely unexpected and it was thought that the 2-(2'-hydroxybenzoyl)-benzoic acid used might possibly have been contaminated with 2-(4'-hydroxybenzoyl)-benzoic acid, although the amount of the latter, even if present, could hardly have been great enough to produce phenolphthalein in the yield stated above. 2-(2'-Hydroxybenzoyl)-benzoic acid was subjected to a very thorough process of purification but when the highly purified acid was used phenolphthalein was obtained again in a yield approximately that given above.

### Experimental Part

**2-Hydroxybenzophenone.**—Salicylic acid was converted into the methyl ether of methyl salicylate,<sup>5</sup> the latter was hydrolyzed to the methyl ether of salicylic acid and the acid was then treated with thionyl chloride.<sup>6</sup> The crude acid chloride, obtained from 80 g. of the methyl ether, was dissolved in 400 cc. of thiophene-free benzene and 80 g. of aluminum chloride was added, in portions, during the course of an hour. After several hours the mixture was decomposed with ice and hydrochloric acid, the benzene layer separated, dried and the excess benzene removed. After the oil had remained at ordinary temperature for several months, 10 g. of crystalline material had formed. The latter was separated and the oil, which consisted to a large extent of 2-hydroxybenzophenone, was distilled with superheated steam; the oily distillate, which solidified when cooled, was recrystallized from alcohol. Sixty grams of 2-hydroxybenzophenone was obtained, m. p. 40–41°.

The crystalline material mentioned above melted at 131–132° after recrystallization from alcohol. It was found to be soluble in aqueous sodium hydroxide, benzene and hot acetic acid and was slightly soluble in ether. It dissolved in concd. sulfuric acid with the formation of a yellow solution. One gram of the material was fused with potassium hydroxide. There was obtained 0.43 g. of a compound which after recrystallization from water melted at 147–148°. This substance proved to be 2,4'-dihydroxybenzophenone, mixed m. p. 147–149°. An analysis and a molecular weight determination of the compound which melted at 131–132° yielded data which correspond to those calculated for  $C_{20}H_{14}O_4$ . The material is probably 2-hydroxy-5-(2'-hydroxybenzoyl)-benzophenone,<sup>7</sup> (A) formed by the further re-



<sup>5</sup> Graebe, *Ann.*, **340**, 210 (1905); Sachs and Herold, *Ber.*, **40**, 2718 (1907).

<sup>6</sup> E. Fischer and Slimmer, *ibid.*, **36**, 2585 (1903).

<sup>7</sup> As a by-product from the synthesis described above Graebe and Ullmann [*ibid.*, **29**, 824 (1896)] obtained a substance which melted at 127° and stated that the analytical results checked most closely to those calculated for a dihydroxybenzophenone.

action of the acid chloride on the primary reaction product, 2-methoxybenzophenone, and subsequent demethylation by the aluminum chloride.

*Anal.* Calcd. for  $C_{20}H_{14}O_4$ : mol. wt., 318; C, 75.46; H, 4.40. Found: mol. wt. (diphenyl),<sup>8</sup> 320; C, 75.35; H, 4.50.

The 4-nitrobenzyl ether of the hydroxy ketone was prepared in the following manner: one hundredth mole of 2-hydroxybenzophenone and 0.01 mole of 4-nitrobenzyl bromide were dissolved in 15 cc. of acetone. One hundredth mole of crystalline sodium hydroxide and 5 cc. of water were added and the mixture heated on a steam-bath for one hour. The ether, which separated in crystalline form, melted at 124–125° after recrystallization from acetone.

**4-Hydroxybenzophenone.**—Twelve and two-tenths grams of benzoic acid, 9.4 g. of phenol and 26 g. of stannic chloride were placed in a flask connected with a reflux condenser and the mixture was heated in a bath at 120° for eighteen hours. After the addition of about 20 cc. of hydrochloric acid, the mixture was filtered. The solid material was treated with 10% aqueous sodium carbonate, which dissolved the benzoic acid and the hydroxybenzophenone. Carbon dioxide was passed into the alkaline solution, whereupon the hydroxy ketone precipitated. The yield of the latter was 4 g.; 6.5 g. of benzoic acid was recovered. After recrystallization of the hydroxy ketone from water, it melted at 135–136°.<sup>9</sup> When an equivalent amount of phenyl benzoate was used in place of benzoic acid, there was obtained 1.5 g. of the ketone and 5 g. of unchanged ester.

**2,4'-Dihydroxybenzophenone.**—(a) A mixture prepared from 10.6 g. of salol and 13 g. of stannic chloride was heated under reflux for eighteen hours at 115–120° in an oil-bath. The reaction product was treated with hot hydrochloric acid in order to remove unchanged stannic chloride, cooled and filtered. After recrystallization from water the hydroxy ketone melted at 147–149°, <sup>10</sup> yield 5.8 g.

(b) Thirteen grams of salicylic acid, 9.4 g. of phenol and 26 g. of stannic chloride were heated under reflux for eighteen hours at 120°. There was obtained 5.5 g. of 2,4'-dihydroxybenzophenone and 4.5 g. of salicylic acid; in one instance we were able to isolate a small quantity of 4,4'-dihydroxybenzophenone.<sup>11</sup>

The dimethyl ether of 2,4'-dihydroxybenzophenone melted at 99–100°.<sup>12</sup>

**3,4'-Dimethoxybenzophenone.**—One hundred thirty-five grams of 3-methoxybenzoic acid<sup>13</sup> was treated with 330 g. of thionyl chloride. After twenty-four hours the excess thionyl chloride was removed under diminished pressure and the acid chloride distilled, b. p. 122–123° under 16 mm. pressure. The yield was 118 g. Eighty-five grams of the acid chloride was dissolved in 50 cc. of tetrachloroethane and added, drop by drop, to a mixture of 65 g. of anisole, 85 g. of aluminum chloride and 100 cc. of tetrachloroethane. After forty-eight hours the reaction mixture was decomposed with ice and hydrochloric acid and the tetrachloroethane and excess anisole removed by steam distillation. The oily product was shaken with 10% sodium hydroxide solution, whereupon it became solid. After recrystallization from alcohol it melted at 58–59°. The yield was practically quantitative.<sup>14</sup>

<sup>8</sup> Purified according to the method of Chipman and Peltier, *Ind. Eng. Chem.*, **21**, 1106 (1929).

<sup>9</sup> Döbner, *Ann.*, **210**, 251 (1881).

<sup>10</sup> Several investigators have reported that this substance melts at 142–144° although Baeyer [*Ann.*, **354**, 178 (1907)] stated that the compound melts at 150–151°.

<sup>11</sup> Michael, *Am. Chem. J.*, **5**, 83 (1883); Baeyer, *Ann.*, **354**, 177 (1907).

<sup>12</sup> Stoermer, *Ber.*, **41**, 323 (1908).

<sup>13</sup> Graebe, *Ann.*, **340**, 211 (1905).

<sup>14</sup> Lea and Robinson [*J. Chem. Soc.*, 2355 (1926)] obtained only a 40% yield of



**2-(2'-Hydroxybenzoyl)- and 2-(4'-Hydroxybenzoyl)-benzoic Acids.**—These compounds were prepared according to the method of Ullmann and Schmidt<sup>15</sup> but we obtained much higher yields and different relative amounts of the two acids. The average result from a number of experiments was as follows. From the interaction of 40 g. of pure phthalic anhydride, 40 g. of phenol and 120 g. of aluminum chloride there were isolated 36 g. of the 4'-hydroxy acid which melted at 205–207°, 16 g. of the 2'-hydroxy acid, m. p. 171–173°, and 4 g. of crude phenolphthalein.

**Attempts to Prepare Isophenolphthalein from 2-(2'-Hydroxybenzoyl)-benzoic Acid.**—In order to obtain 2-(2'-hydroxybenzoyl)-benzoic acid entirely free from the 4'-hydroxy isomer, the former acid was recrystallized four times from methyl alcohol, converted into the ethyl ester and the latter hydrolyzed; the acid obtained melted at 171–173°.

The pure 2-(2'-hydroxybenzoyl)-benzoic acid, prepared as described above, was condensed with phenol according to the method of Orndorff and Barrett.<sup>16</sup> There was obtained phenolphthalein in 40% yield, a small amount of fluoran and a tar. When the phenolphthalein was fused with potassium hydroxide, 4,4'-dihydroxybenzophenone was isolated in 85% yield.

**Methylation of Phenolphthalein and Demethylation of Phenolphthalein Dimethyl Ether.**—Fifteen grams of phenolphthalein was dissolved in 200 cc. of 10% sodium hydroxide solution and 35 cc. of dimethyl sulfate was added, in portions, while the mixture was shaken vigorously. Ten grams of sodium hydroxide was added and the solution heated for one-half hour under reflux. An oil separated which became solid when cooled. After recrystallization from alcohol the phenolphthalein dimethyl ether<sup>17</sup> melted at 101–102°; yield 14.7 g. or 90% of the calculated amount.

Demethylation was effected in the following manner. Five grams of the ether, 40 cc. of acetic acid and 25 cc. of 48% hydrobromic acid were refluxed for five hours in a flask fitted to a reflux condenser by means of a ground-glass connection. Most of the hydrobromic and acetic acid was removed by distillation under diminished pressure. The yield of crude phenolphthalein was 3.8 g.; after recrystallization from dilute alcohol it melted at 252–253°.

The ether can also be demethylated if a mixture, prepared from 1 g. of the material, 30 cc. of dry thiophene-free benzene and 2.2 g. of aluminum chloride, is refluxed for two hours.

**Preparation of Tertiary Carbinols.**—The tertiary carbinols were prepared by the action of 2-methylphenylmagnesium bromide and 2-ethoxymethylphenylmagnesium bromide, respectively, on various ketones. 2-Ethoxymethylbromobenzene, necessary for the preparation of the Grignard reagent, was obtained in the following manner. Two hundred and fifty grams of pure 2-bromotoluene was brominated in a flask connected to a reflux condenser by means of a ground-glass connection.<sup>18</sup> The 2-bromobenzyl bromide, which boiled at 130–136° under 16 mm. pressure, was used for the subsequent procedure. One hundred and twenty-six grams of 2-bromobenzyl bromide was added to a cold solution of sodium ethylate prepared from 250 cc. of absolute alcohol and 14 g. of the ketone, possibly due to the fact that carbon disulfide was used as a solvent; they reported the melting point to be 55°.

<sup>15</sup> Ullmann and Schmidt, *Ber.*, **52**, 2106 (1919). See also Thiel and Müller, *ibid.*, **55**, 1314 (1922).

<sup>16</sup> Orndorff and Barrett, *J. Am. Chem. Soc.*, **46**, 2488 (1924).

<sup>17</sup> This compound has been obtained by Grande, *Gazz. chim. ital.*, **26**, I, 223 (1896); Underwood and Barker, *J. Am. Chem. Soc.*, **52**, 4084 (1930), and by Herzig and Meyer, *Monatsh.*, **17**, 430 (1896).<sup>9</sup>

<sup>18</sup> Jackson, *Am. Chem. J.*, **1**, 101 (1879–1880).

TABLE I  
TERTIARY CARBINOLS

The letter in parentheses before the ketone indicates the Grignard reagent used: A, 2-methylphenylmagnesium bromide; B, 2-ethoxymethylphenylmagnesium bromide.

| Carbinol obtained, <sup>a</sup><br>-triphenylcarbinol | Grignard reagent and<br>substituted benzophenone | Color with<br>H <sub>2</sub> SO <sub>4</sub> | M. p., °C.           | Formula                                        | Calcd., %<br>C H | Found, %<br>C H |
|-------------------------------------------------------|--------------------------------------------------|----------------------------------------------|----------------------|------------------------------------------------|------------------|-----------------|
| 1 2-Methyl-                                           | (A) Benzophenone                                 | Yellow                                       | 100-101 <sup>b</sup> | C <sub>20</sub> H <sub>18</sub> O              | ...              | ...             |
| 2 2-Methyl-2',4''-dimethoxy-                          | (A) 2,4'-Dimethoxy-                              | Orange                                       | 152-154              | C <sub>22</sub> H <sub>22</sub> O <sub>3</sub> | 79.04 6.59       | 78.89 6.67      |
| 3 2-Methyl-4,4''-dimethoxy-                           | (A) 4,4'-Dimethoxy- <sup>e</sup>                 | Orange                                       | 109-110              | C <sub>22</sub> H <sub>22</sub> O <sub>3</sub> | 79.04 6.59       | 78.70 6.75      |
| 4 2-Ethoxymethyl-                                     | (B) Benzophenone                                 | Yellow                                       | 81- 82               | C <sub>22</sub> H <sub>22</sub> O <sub>2</sub> | 83.02 6.92       | 83.10 6.88      |
| 5 2-Ethoxymethyl-2'-methoxy-                          | (B) 2-Methoxy-                                   | Green turns<br>to red                        | 108-109              | C <sub>23</sub> H <sub>24</sub> O <sub>3</sub> | 79.27 6.90       | 79.26 6.90      |
| 6 2-Ethoxymethyl-3'-methoxy-                          | (B) 3-Methoxy- <sup>d</sup>                      | .....                                        | Oily                 | C <sub>23</sub> H <sub>24</sub> O <sub>3</sub> | 79.27 6.90       | .. ..           |
| 7 2-Ethoxymethyl-4'-methoxy-                          | (B) 4-Methoxy-                                   | Orange                                       | 100-101              | C <sub>23</sub> H <sub>24</sub> O <sub>3</sub> | 79.27 6.90       | 79.10 6.98      |
| 8 2-Ethoxymethyl-2',2''-dimethoxy-                    | (B) 2,2'-Dimethoxy- <sup>e</sup>                 | Blue turns to<br>purple                      | 103-104              | C <sub>24</sub> H <sub>26</sub> O <sub>4</sub> | 76.19 6.88       | 76.06 6.94      |
| 9 2-Ethoxymethyl-2',4''-dimethoxy-                    | (B) 2,4'-Dimethoxy-                              | Red                                          | 107-108              | C <sub>24</sub> H <sub>26</sub> O <sub>4</sub> | 76.19 6.88       | 75.97 6.93      |
| 10 2-Ethoxymethyl-4',4''-dimethoxy-                   | (B) 4,4'-Dimethoxy-                              | Orange-red                                   | 74- 76               | C <sub>24</sub> H <sub>26</sub> O <sub>4</sub> | 76.19 6.88       | 75.80 6.67      |
| 11 2-Ethoxymethyl-3',4''-dimethoxy-                   | (B) 3,4'-Dimethoxy-                              | Orange-red                                   | 83- 84               | C <sub>24</sub> H <sub>26</sub> O <sub>4</sub> | 76.19 6.88       | 75.82 7.10      |
| 12 9-(2'-Methylphenyl)-xanthrol <sup>f</sup>          | (A) Xanthone                                     | Yellow                                       | 165-166              | C <sub>20</sub> H <sub>16</sub> O <sub>2</sub> | 83.33 5.56       | 83.40 5.65      |
| 13 9-(2'-Ethoxymethylphenyl)-<br>xanthrol             | (B) Xanthone                                     | Yellow                                       | 153-154              | C <sub>22</sub> H <sub>20</sub> O <sub>3</sub> | 79.52 6.02       | 79.44 6.06      |

<sup>a</sup> Carbinols 1, 2, 7, 9 and 12 were recrystallized from a mixture of benzene and petroleum ether (30-60°); 4 and 5 from a mixture of high (90-120°) and low boiling petroleum ether (30-60°); 8 and 11 from methyl alcohol, 13 from benzene and 3 and 10 from alcohol. <sup>b</sup> Bistrzycki and Gyr, *Ber.*, 37, 1248 (1904), recorded the melting point as 98°. <sup>c</sup> Bayer and Burkhardt, *Ann.*, 202, 126 (1880); Zincke and Birschell, *ibid.*, 362, 226 (1908); Blicke and Smith, *J. Am. Chem. Soc.*, 51, 1872 (1929). <sup>d</sup> Ullmann and Goldberg, *Ber.*, 35, 2814 (1902). <sup>e</sup> Richter, *J. prakt. Chem.* [2] 28, 285 (1883); Graebe and Feer, *Ber.*, 19, 2810 (1886). <sup>f</sup> Decker and Fellenberg, *Ann.*, 356, 309 (1907), obtained a compound from xanthone and 2-tolylmagnesium bromide which they claimed was 9-(2'-methylphenyl)-xanthrol. Their material consisted of "pseudo crystals" which melted at 150.5°. The product obtained by us consisted of well-defined colorless glistening crystals.



sodium. The mixture was heated for two hours on a steam-bath. The sodium bromide was removed and the greater part of the alcohol distilled. The residue was poured into water and the oil which separated was treated successively with a concd. sodium bisulfite solution,<sup>19</sup> water and dilute aqueous sodium carbonate. The oil was dried and distilled; b. p. 108–109° under 13 mm. pressure.

To the Grignard reagent prepared from 0.1 mole of 2-methylbromobenzene or 2-ethoxymethylbromobenzene, 0.1 mole of magnesium, a few crystals of iodine and a mixture composed of 25 cc. of ether and 25 cc. of dry benzene, there was added 0.07 mole of the ketone, dissolved or suspended in 50 cc. of dry benzene. During the preparation of the Grignard reagent a stream of dry nitrogen was passed over the top of the condenser. The mixture was heated on a steam-bath for three hours and then decomposed with ice and ammonium chloride. The crude carbinols were subjected to steam distillation for several hours, then dried and purified by recrystallization.

The carbinols which were prepared are listed below. The method of preparation is indicated in Table I.

**Oxidation of Tertiary Carbinols to Dimethyl Ethers of Diarylphthalides.**—In many instances the oxidation of the methyl group to carboxyl in the carbinols which contained a tolyl nucleus did not take place readily and we were able, only in a few cases, to prepare the desired phthalide from such carbinols. The oxidation of 9-(2'-methylphenyl)-xanthidrol to fluoran was accomplished as follows. A solution prepared from 0.50 g. of the carbinol, 20 cc. of concd. sulfuric acid and 50 cc. of water was heated to the boiling point. Five-tenths of a gram of sodium dichromate, dissolved in 5 cc. of water, was added to the hot solution. The latter was stirred thoroughly and boiled for ten minutes. The mixture was cooled, water was added and the solid material removed by filtration.

TABLE II  
DIMETHYL ETHERS OF DIARYLPHTHALIDES

| Carbinol | Oxidation product <sup>a</sup>    | M. p., °C.           |
|----------|-----------------------------------|----------------------|
| 1, 4     | Diphenylphthalide                 | 114–115 <sup>b</sup> |
| 5        | 2'-Methoxydiphenylphthalide       | 127–128              |
| 6        | 3'-Methoxydiphenylphthalide       | Gum                  |
| 7        | 4'-Methoxydiphenylphthalide       | Gum <sup>c</sup>     |
| 8        | 2',2''-Dimethoxydiphenylphthalide | 151–152 <sup>d</sup> |
| 9        | 2',4''-Dimethoxydiphenylphthalide | 127–128 <sup>e</sup> |
| 10       | 4',4''-Dimethoxydiphenylphthalide | 101–102 <sup>f</sup> |
| 11       | 3',4''-Dimethoxydiphenylphthalide | 200–201 <sup>g</sup> |
| 12, 13   | Fluoran                           | 182–183 <sup>h</sup> |

<sup>a</sup> All of the ethers were recrystallized from alcohol except the compound obtained from carbinol 11; this substance was recrystallized from toluene. <sup>b</sup> V. Pechmann [*Ber.*, **14**, 1866 (1881)] recorded the melting point as 115°. <sup>c</sup> H. Meyer and O. Fischer [*ibid.*, **44**, 1953 (1911)] stated that this compound melts at 86°; they experienced difficulty in obtaining it in crystalline form. <sup>d</sup> Ferrario [*Gazz. chim. ital.*, **41**, I, 1 (1911)] stated that this substance melts at 145–146°. <sup>e</sup> Orndorff and Barrett [*J. Am. Chem. Soc.*, **46**, 2490 (1924)] found the melting point to be 122°. <sup>f</sup> Grande [*Gazz. chim. ital.*, **26**, I, 224 (1896)] recorded the melting point as 101–102°. <sup>g</sup> This compound is insoluble in ether, soluble in hot toluene and dissolves in concd. sulfuric acid with the formation of a violet solution. *Anal.* Calcd. for C<sub>22</sub>H<sub>18</sub>O<sub>4</sub>: C, 76.29; H, 5.24. Found: C, 75.94; H, 5.17. <sup>h</sup> Ferrario [*Gazz. chim. ital.*, **41**, I, 10 (1911)] recorded the melting point as 182°.

<sup>19</sup> To remove any aldehyde present; Errera, *Gazz. chim. ital.*, **17**, 204, 208 (1887).

TABLE III

## HYDROXYDIARYLPHTHALIDES

Prepared by demethylation of the oxidation products (dimethyl ethers of diarylphthalides) listed in Table II.<sup>a</sup>

|                |                                   | M. p., °C.             |
|----------------|-----------------------------------|------------------------|
| 7 <sup>b</sup> | 4'-Hydroxydiphenylphthalide       | Amorphous              |
| 8              | Fluoran                           | 182-183 <sup>c</sup>   |
| 9              | Isophenolphthalein                | 198-199 <sup>d</sup>   |
| 10             | Phenolphthalein                   | 254-255 <sup>e</sup>   |
| 11             | 3',4''-Dihydroxydiphenylphthalide | Amorphous <sup>f</sup> |

<sup>a</sup> Demethylation was effected with hydrobromic acid in the manner described in the case of phenolphthalein dimethyl ether. <sup>b</sup> These numbers refer to the tertiary carbinols from which the hydroxydiarylphthalides were obtained. <sup>c</sup> Ferrario [*Gazz. chim. ital.*, **41**, I, 10 (1911)] recorded the melting point as 182°. <sup>d</sup> Orndorff and Barrett [*J. Am. Chem. Soc.*, **46**, 2485 (1924)] stated that the compound melted at 200°. <sup>e</sup> Bebie [*J. Am. Pharm. Assoc.*, **19**, 372 (1930)] reported the melting point as 262.8° (corr.). <sup>f</sup> This material dissolved in alkali to form a red solution.

After recrystallization from alcohol, there was obtained 0.22 g. of crystalline fluoran; mixed m. p. 181-182°.

The oxidation of the ethoxymethyl group to carboxyl is illustrated by the conversion of 2-ethoxymethyl-4',4''-dimethoxytriphenylcarbinol into the dimethyl ether of phenolphthalein. Five grams of the carbinol, 10.5 g. of finely powdered sodium dichromate and 100 cc. of acetic acid were refluxed for two hours. The mixture was treated with 400 cc. of hot water and after some time the gummy precipitate was removed and recrystallized from alcohol. Three and one-tenth grams of material was obtained which melted at 97-99°. After further recrystallization the phenolphthalein dimethyl ether melted at 101-102°; yield 70% of the calculated amount.

The yields obtained in the oxidation of other carbinols varied from 40-60%. In the case of some of the dimethoxydiarylphthalides considerable difficulty was experienced in their purification.

The oxidation products obtained from other carbinols are recorded in Table II.

## Summary

It has been found that the interaction of 2-ethoxymethylphenylmagnesium bromide with the methyl ethers of various hydroxybenzophenones yields tertiary carbinols in which the ethoxymethyl group can be oxidized to carboxyl with the spontaneous formation of methyl ethers of diarylphthalides. Upon demethylation hydroxydiarylphthalides are obtained.

This method is of advantage in that phthalides so formed cannot be contaminated with isomeric phthalides or anthraquinone compounds and, due to the method of synthesis, the positions of any substituents in the phthalide molecule are known with certainty.

This procedure has been found satisfactory for the preparation of diphenylphthalide, phenolphthalein, isophenolphthalein and fluoran.

Preliminary tests indicate that isophenolphthalein has no laxative effect on humans.



## PART II

### THE PREPARATION OF 2-(4'-HYDROXYBENZOYL)-4'-HYDROXYBENZOPHENONE

The preparation of phenolphthalein dimethyl ether (4',4''-dimethoxydiphenylphthalide) was attempted from phthalic anhydride and 4-methoxyphenylmagnesium iodide. Bauer<sup>1</sup> prepared diphenylphthalide in good yield from phthalic anhydride and phenylmagnesium bromide<sup>2</sup> and by the use of the anhydride mentioned above and 2-methoxyphenylmagnesium iodide Ferrario<sup>3</sup> obtained 2',2''-dimethoxydiphenylphthalide which, upon demethylation, yielded fluorane.

From phthalic anhydride and 4-methoxyphenylmagnesium iodide, and also from the methyl ester of 2-(4'-methoxybenzoyl)-benzoic acid and the Grignard reagent, we obtained a product which melted at 157–159°; after demethylation the material melted at 225–226° and dissolved in alkali to form a pale yellow solution. The melting points of phenolphthalein dimethyl ether and of phenolphthalein are 102–103° and 254–255°, respectively. Since the data obtained from an analysis and a molecular weight determination of the product which melted at 157–159° corresponded to that calculated for phenolphthalein dimethyl ether, it was evident that a substance isomeric with the last-named compound had been formed.

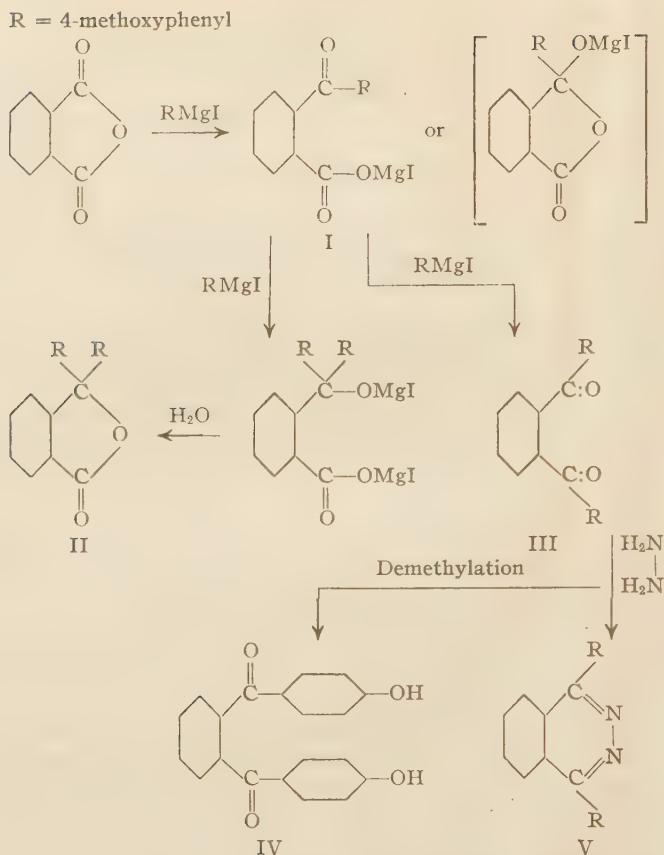
A consideration of the possible ways in which phthalic anhydride and 4-methoxyphenylmagnesium iodide may combine shows that after the interaction of equivalent amounts of these substances with the formation of compound I, further reaction of the latter with the Grignard reagent may yield either the dimethyl ether of phenolphthalein (II) or the dimethyl ether of 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone (III), a substance isomeric with phenolphthalein dimethyl ether.

The chemical behavior of the compound (m. p. 157–159°) obtained conformed entirely with that of a substance of structure III. A 1,2-diazine-3,6-di-(*p*-methoxyphenyl)-4,5-benzopyridazine (V), obtained by the action of hydrazine, a dioxime and a diphenylhydrazone were prepared and analyzed. When the compound was fused with potassium hydroxide, 4-methoxybenzoic acid was obtained.

<sup>1</sup> Bauer, *Ber.*, **38**, 240 (1905).

<sup>2</sup> When 4-methoxyphenylmagnesium bromide was used this investigator isolated only gummy material as a reaction product.

<sup>3</sup> Ferrario, *Gazz. chim. ital.*, **41**, I, 1 (1911).



Demethylation of **III** yielded 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone (**IV**). This substance, when fused with potassium hydroxide, yielded two molecular equivalents of 4-hydroxybenzoic acid.

A number of years ago Baeyer<sup>4</sup> reduced diphenylphthalide (**VI**) to triphenylmethane-2-carboxylic acid (diphenylphthalin, **VII**). The latter, when treated with concentrated sulfuric acid, yielded a substance which, although it was not isolated in pure form nor was its structure suggested,<sup>5</sup> upon oxidation was converted into 9-hydroxy-9-phenylanthrone-10 (**IX**). Since Haller and Guyot<sup>6</sup> obtained this same compound (**IX**) from the action of phenylmagnesium bromide on anthraquinone, and these investigators,<sup>7</sup> as well as Liebermann,<sup>8</sup> were able to prepare the corresponding

<sup>4</sup> Baeyer, *Ann.*, **202**, 100 (1880).

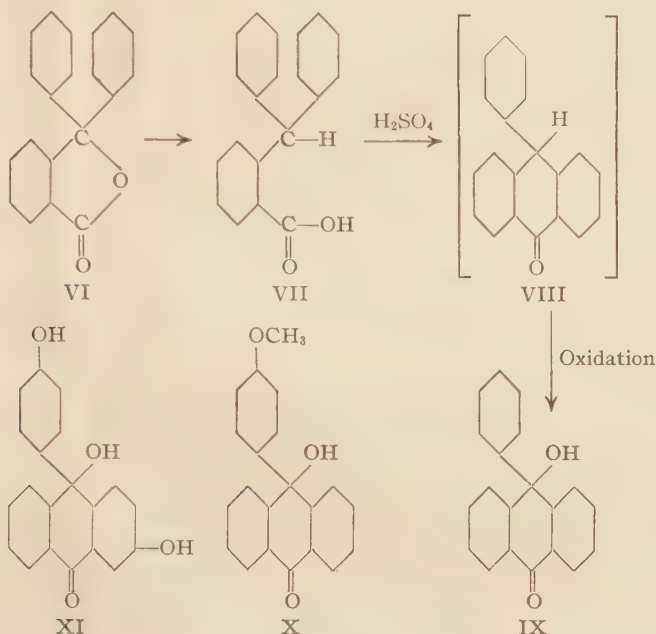
<sup>5</sup> Presumably this material was 9-phenylanthrone-10 (**VIII**).

<sup>6</sup> Haller and Guyot, *Bull. soc. chim.*, [3] **31**, 797 (1904).

<sup>7</sup> Haller and Guyot, *Compt. rend.*, **121**, 102 (1895).

<sup>8</sup> Liebermann, Glawe and Lindenbaum, *Ber.*, **37**, 3337 (1904).

carbinol chloride, there seems to be no doubt regarding the structure of this substance.



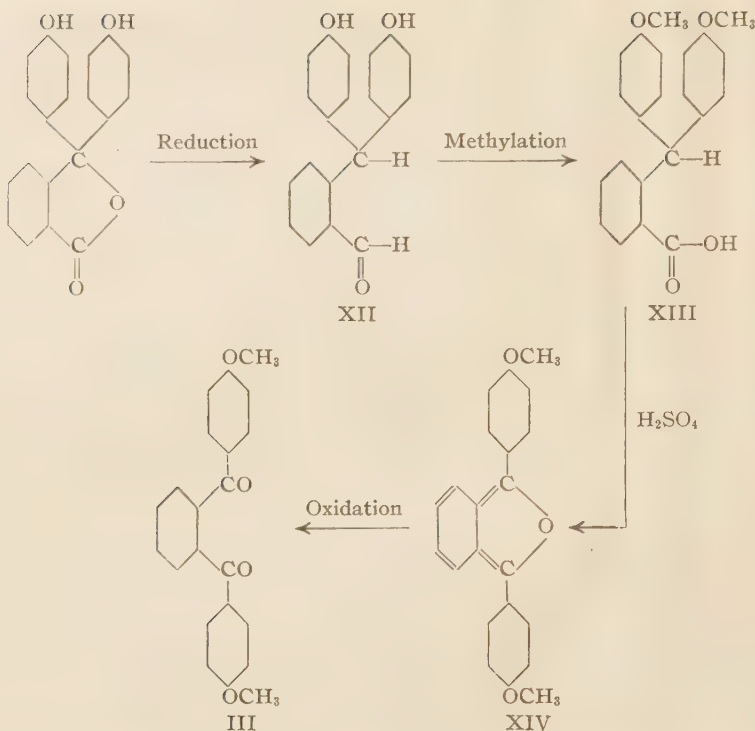
We found that 4-methoxyphenylmagnesium iodide reacts with anthraquinone, analogous to phenylmagnesium bromide, to form 9-(4'-methoxyphenyl)-9-hydroxyanthrone-10 (X).

It might be expected that phenolphthalein-4',4''-dihydroxydiphenylphthalide—when subjected to the same series of reactions applied in the case of diphenylphthalide, would yield a dihydroxy analog of IX, namely, 3,9-dihydroxy-9-(4'-hydroxyphenyl)-anthrone-10 (XI) and Baeyer<sup>5</sup> considered the compound obtained by him from phenolphthalein to possess structure XI. However, since we found that the product obtained from phenolphthalein by Baeyer's method yielded neither a carbinol chloride nor a fuchsone when treated with hydrogen chloride, the structure previously assigned to the compound (XI) seemed questionable. It was discovered that Baeyer's compound<sup>9</sup> is not an anthranol but is identical with 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone (IV).

When phenolphthalein was reduced to 4',4''-dihydroxytriphenylmethane-2-carboxylic acid (phenolphthalin, XII), the latter converted into the dimethyl ether (XIII) and then treated as described in the case of diphenylphthalin, the final reaction product was found to be identical with compound III. In this instance we were able to isolate the yellow

<sup>9</sup> Named by him "dihydroxyphenylanthranol" according to the older nomenclature.





intermediate reaction product 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran (XIV).<sup>10</sup>

### Experimental Part

2-(4''-Hydroxybenzoyl)-4'-hydroxybenzophenone. (a) From Phthalic Anhydride and 4-Methoxyphenylmagnesium Iodide.—4-Methoxyphenylmagnesium iodide was prepared from 18.8 g. of 4-iodoanisole, 2 g. of magnesium, 30 cc. of ether and 30 cc. of dry benzene. Four and seven-tenths grams of phthalic anhydride, dissolved in 100 cc. of benzene, was stirred rapidly and the Grignard reagent added to it. The mixture was heated for twelve hours. The precipitate which had formed was removed by filtration and decomposed with ice and ammonium chloride. The product was extracted with benzene and the benzene layer shaken with 10% sodium carbonate solution. After removal of the solvent the solid residue was recrystallized from toluene; m. p. 157–159°. This substance, the dimethyl ether of 2-(4''-hydroxybenzoyl)-4'-hydroxybenzo-

<sup>10</sup> The diphenyl analog of this substance has been prepared from phenylphthalide and phenylmagnesium bromide by Guyot and Catel [*Bull. soc. chim.*, [3] **35**, 1136 (1906)], Guyot and Vallette [*Ann. chim. phys.*, [8] **23**, 372, 388 (1911)] and by Seer and Dischendorfer [*Monatsh.*, **34**, 1495 (1913)]. It has been shown by Guyot and Haller [*Ann. chim. phys.*, [8] **19**, 297 (1910)] that 2-bis-(*p*-dimethylaminophenyl)-phthalide, upon reduction, treatment of the reduced material with acetic acid and finally oxidation of the reaction product, yields 2-(4''-dimethylaminobenzoyl)-4'-dimethylaminobenzophenone; hence the above-mentioned diarylphthalide behaves entirely analogous to phenolphthalein.

phenone, is somewhat soluble in hot alcohol and insoluble in ether. It was demethylated with hydrobromic acid in acetic acid solution.

2-(4''-Hydroxybenzoyl)-4'-hydroxybenzophenone, after recrystallization from acetic acid and then from dilute alcohol, melted at 225–226°. The material is insoluble in ether and benzene.

*Anal.* Calcd. for  $C_{20}H_{14}O_4$ : mol. wt., 318; C, 75.47; H, 4.40. Found: mol. wt. (alcohol),<sup>11</sup> 322; C, 75.31; H, 4.40.

(b) From the Methyl Ester of 2-(4'-Methoxybenzoyl)-benzoic Acid and 4-Methoxyphenylmagnesium Iodide.—The Grignard reagent, prepared from 11.7 g. of 4-iodoanisole, 1.2 g. of magnesium, 25 cc. of ether and 25 cc. of benzene, was added to 10.8 g. of the substituted benzoic acid dissolved in 30 cc. of benzene. The mixture was heated for four hours and then decomposed in the usual manner. The dimethyl ether obtained melted at 157–159°.

(c) From Phenolphthalein.—4',4''-Dihydroxytriphenylmethane-2-carboxylic acid (phenolphthalein) was prepared from U. S. P. phenolphthalein in 96% yield; m. p. 231–232°.<sup>12</sup>

Two hundred and fifty cubic centimeters of concd. sulfuric acid was poured into a beaker and stirred rapidly. Two hundred grams of finely powdered phenolphthalein was added in one portion. After the mixture had been stirred for five minutes the solid material had all dissolved. The solution was then poured into two liters of cold water which was stirred rapidly. The green, granular precipitate was filtered and washed with water. This product dissolved readily in acetone, alcohol, benzene and ether with the formation of solutions which exhibited a strong green fluorescence. The material was dissolved immediately in a mixture of 500 cc. of water and 80 g. of sodium hydroxide. The orange red solution was stirred and a solution prepared from 75 g. of potassium permanganate, 50 g. of sodium hydroxide and 1000 cc. of water was added. After five minutes the manganese salt was removed by filtration. The filtrate was stirred and treated with dilute hydrochloric acid. The precipitated material was filtered, washed with water, dried, recrystallized several times from acetic acid and then from dilute methyl alcohol. Since some of the product remains dissolved in the acetic acid mother liquors, the latter should be concentrated. The yield of the substituted benzophenone was 66 g.; m. p. 224–225°.<sup>13</sup>

(d) From 4',4''-Dimethoxytriphenylmethane-2-carboxylic Acid.—This acid,<sup>14</sup> "prepared from phenolphthalein dimethyl ether," when subjected to the action of sulfuric acid in the manner described above, yielded an intensely yellow material, 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran (XIV). After recrystallization from a mixture of acetone and alcohol the compound melted at 126–127°. The compound dissolves in ether, benzene and acetic acid to form solutions which possess a green fluorescence.

*Anal.* Calcd. for  $C_{22}H_{16}O_5$ : mol. wt., 330; C, 80.00; H, 5.45. Found: mol. wt. (benzene),<sup>11</sup> 324; C, 79.78; H, 5.43.

The furan, when oxidized, yielded the dimethyl ether of 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone. Six-tenths of a gram of the furan, dissolved in 10 cc. of hot acetic acid, was mixed with 1 g. of sodium dichromate, 10 cc. of acetic acid and 1 cc. of sulfuric acid. The mixture was heated for ten minutes on a steam-bath. Twenty

<sup>11</sup> Menzies method.

<sup>12</sup> Baeyer, *Ann.*, 202, 81 (1880).

<sup>13</sup> Baeyer [*ibid.*, 202, 102 (1880)] recorded the melting point as 212°. We obtained this melting point but after further purification the material melted at the temperature stated above.

<sup>14</sup> Grande, *Gazz. chim. ital.*, 26, I, 228 (1896).

cubic centimeters of hot water was added and the crystalline precipitate obtained was recrystallized from alcohol. The yield was 0.4 g.; m. p. 157–159°; mixed m. p. 157–159°.

**Alkali Fusions.**—One gram of 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone was fused with 5 g. of potassium hydroxide. The residue was dissolved in a small amount of water, filtered and acidified. Sixty-two hundredths of a gram of 4-hydroxybenzoic acid precipitated; m. p. 209–211°. From the filtrate 0.18 g. more of the acid was obtained upon extraction with ether.

When the dimethyl ether of the substituted benzophenone was fused with potassium hydroxide, 4-methoxybenzoic acid was formed; m. p. 181–183°.

**Derivatives of 2-(4'-Methoxybenzoyl)-4'-methoxybenzophenone.** 3,6-Di-(*p*-methoxyphenyl)-4,5-benzopyridazine (V).—Three and five-tenths grams of the benzophenone was mixed with 20 cc. of acetic acid and to the hot solution there was added, in small portions, a solution prepared from 5 g. of 40% aqueous hydrazine hydrate and 10 cc. of acetic acid. The mixture was refluxed for two hours, an equal volume of water added, the solution cooled, the precipitate filtered and washed with water. Three and three-tenths grams of the diazine was obtained. After recrystallization from acetone the compound melted at 205–206°. It is insoluble in ether but soluble in warm benzene.

*Anal.* Calcd. for  $C_{22}H_{13}O_2N_2$ : C, 77.18; H, 5.30; N, 8.19. Found: C, 76.89; H, 5.30; N, 8.10.

**Dioxime.**—A solution prepared from 5 g. of hydroxylamine hydrochloride, 100 cc. of methyl alcohol and 10 g. of sodium hydroxide was added to 3.7 g. of the benzophenone dissolved in 100 cc. of methyl alcohol. The mixture was refluxed for two hours, cooled, the precipitate filtered and washed with 50% methyl alcohol. After recrystallization from ethyl alcohol there was obtained 2.3 g. of the oxime, which melted at 177–178° with decomposition. The compound is insoluble in ether and benzene.

*Anal.* Calcd. for  $C_{22}H_{20}O_4N_2$ : C, 70.20; H, 5.36; N, 7.45. Found: C, 70.61; H, 5.31; N, 7.79.

**Diphenylhydrazone.**—A solution prepared from 2.4 g. of the benzophenone, 4.3 g. of phenylhydrazine and 25 cc. of alcohol was refluxed for twelve hours. The solution was cooled, the precipitate filtered and washed with alcohol. After recrystallization from alcohol, 1 g. of material was obtained which melted with decomposition at 171–173°. The product is soluble in warm benzene but insoluble in ether.

*Anal.* Calcd. for  $C_{34}H_{30}O_2N_4$ : C, 77.53; H, 5.76; N, 10.64. Found: C, 77.37; H, 5.74; N, 10.83.

## Summary

The dimethyl ether of 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone has been prepared by four methods: (a) from phthalic anhydride and 4-methoxyphenylmagnesium iodide; (b) from the methyl ester of 2-(4'-methoxybenzoyl)-benzoic acid and the Grignard reagent mentioned above; (c) from phenolphthalein; (d) from 4',4''-dimethoxytriphenylmethane-2-carboxylic acid. The corresponding dihydroxy ketone was obtained by demethylation of the ether.

The compound described in the literature as "dihydroxyphenylanthranol," according to modern nomenclature 3,9-dihydroxy-9-(4'-hydroxyphenyl)-anthrone-10, is in reality 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone.



### PART III

#### THE PREPARATION OF SEVERAL SUBSTITUTED ANTHRONES

In view of the fact that 9-hydroxy-9-phenylanthrone-10 (phenyl-oxanthranol)<sup>1</sup> and 9,9-diphenylanthrone-10<sup>1b,2</sup> have been isolated as reaction products from the interaction of phthalyl chloride and benzene, it seemed not improbable that corresponding hydroxy compounds, namely, 3,9-dihydroxy-9-(4'-hydroxyphenyl)-anthrone-10 (I), 3-hydroxy-9,9-di-(4'-hydroxyphenyl)-anthrone-10 (II) and possibly, in addition, 3-hydroxy-9,9,10-tri-(4'-hydroxyphenyl)-9,10-dihydroanthrol-10 (III) might be formed as by-products from the condensation of phthalic anhydride with phenol. Since the cathartic action of yellow phenolphthalein may be due to the presence of these compounds, we wished to prepare them in order that they might be tested for laxative action.

Although Baeyer<sup>3</sup> stated that he had obtained compound I, called by him "dihydroxyphenylanthranol," from phenolphthalein it has been shown that Baeyer's compound is, in reality, 2-(4"-hydroxybenzoyl)-4'-hydroxybenzophenone.

We have not been able, as yet, to obtain the first three substances mentioned above but the methyl ethers of the corresponding 2-hydroxy compounds XI, XV and XVI as well as several other anthraquinone derivatives have been prepared. Upon demethylation of the methoxy derivatives highly colored, gummy or resinous products were obtained, undoubtedly fuchsones, which proved to be very difficult to purify.

It was found that interaction of 4-methoxyphenylmagnesium iodide with anthraquinone and with 2-methoxyanthraquinone yields 9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10 (IV) and 2-methoxy-9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10 (XI), respectively. In the case of the latter compound it was necessary to prove that the Grignard reagent had reacted with carbonyl 9 in the methoxyanthraquinone and not with carbonyl 10; therefore the substance was synthesized according to the scheme shown.

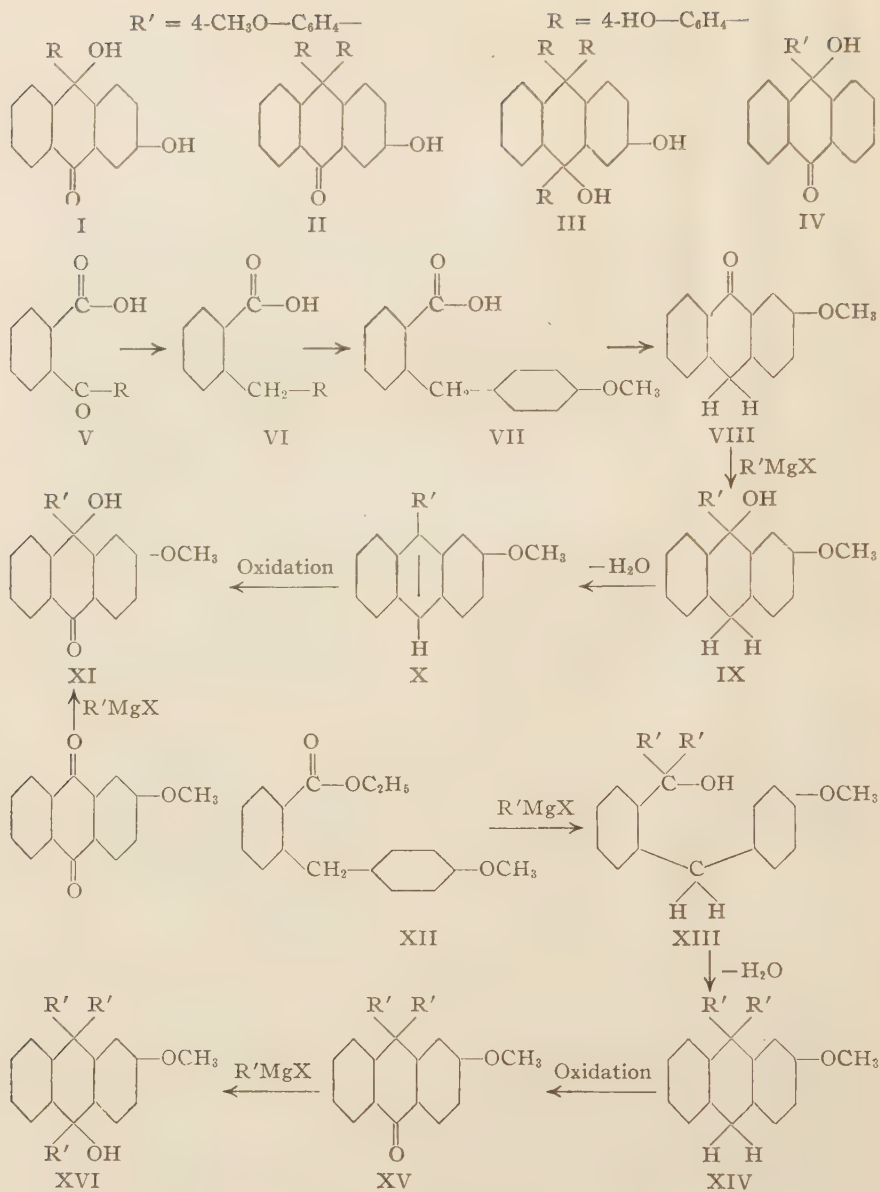
2-Methoxy-9,9-di-(4'-methoxyphenyl)-anthrone-10 (XV) and 2-methoxy-9,9,10-tri-(4'-methoxyphenyl)-9,10-dihydroanthrol-10 (XVI) were obtained by means of the reactions indicated.

<sup>1</sup> (a) Copisarow, *J. Chem. Soc.*, **111**, 10 (1917); (b) **117**, 209 (1920).

<sup>2</sup> Haller and Guyot, *Bull. soc. chim.*, [3] **17**, 873 (1897).

<sup>3</sup> Baeyer, *Ann.*, **202**, 100 (1880).

<sup>4</sup> Blicke and Weinkauff, *J. Am. Chem. Soc.*, **54**, 1446 (1932).



The ether-benzene solution was separated, filtered, dried and the solvents removed. The solid residue, after recrystallization from alcohol, melted at 206–207°. The material dissolved in concd. sulfuric acid with the formation of a dark green solution.

*Anal.* Calcd. for  $C_{21}H_{16}O_3$ : mol. wt., 316; C, 79.74; H, 5.06;  $OCH_3$ , 8.8. Found: mol. wt. (benzene),<sup>5</sup> 314; C, 79.41; H, 5.00;  $OCH_3$ , 9.8.<sup>6</sup>

**2-(4'-Hydroxybenzyl)-benzoic Acid (VI).**—The following method is a modification of that reported by Bistrzycki and Yssel de Schepper.<sup>7</sup> A solution prepared from 150 g. of 2-(4'-hydroxybenzoyl)-benzoic acid and 2.5 liters of 10% aqueous sodium hydroxide was heated on a steam-bath and stirred rapidly. One hundred and fifty grams of zinc dust was added and the mixture was heated for twenty hours. After filtration the filtrate was acidified and the product recrystallized from alcohol; m. p. 153–154°;<sup>8</sup> yield, 114 g.

**2-Hydroxyanthraquinone from 2-Hydroxyanthrone-9.**—Thirty grams of 2-hydroxyanthrone-9,<sup>8</sup> prepared from 2-(4'-hydroxybenzyl)-benzoic acid, was suspended in 150 cc. of acetic acid and treated with 32 g. of sodium dichromate, dissolved in 15 cc. of hot water, in a flask fitted with a reflux condenser. The mixture soon began to boil. After some time the flask was heated on a steam-bath for about ten minutes, cooled, the crystalline reaction product filtered, washed with acetic acid and then with water. The material weighed 30 g. and melted at 303–304°.<sup>9</sup>

**2-Methoxyanthrone-9 (VIII).**—Since difficulties were encountered in the methylation of 2-hydroxyanthraquinone, the methyl ether of the latter substance was prepared by an indirect method.

The methyl ester of 2-(4'-methoxybenzyl)-benzoic acid (VII) was obtained from 45.6 g. of 2-(4'-hydroxybenzyl)-benzoic acid, 160 cc. of 10% sodium hydroxide solution and 40 cc. of dimethyl sulfate. The ester separated as an oil. In order to hydrolyze the ester, 25 g. of sodium hydroxide was added to the reaction mixture and the latter was refluxed for several hours. The clear, cold solution was acidified. After recrystallization from alcohol the 2-(4'-methoxybenzyl)-benzoic acid melted at 116–117°;<sup>10</sup> yield, 94% of the calculated amount.

Forty-eight and four-tenths grams of finely powdered 2-(4'-methoxybenzyl)-benzoic acid was dissolved in 250 cc. of concd. sulfuric acid which had been cooled to 5°. At the end of three minutes the temperature of the mixture had risen to 25°. The solution was poured immediately into 1.5 liters of ice water. The product was filtered, washed with water and recrystallized from methyl alcohol; m. p. 94–95°; yield of pure product, 30 g.

*Anal.* Calcd. for  $C_{16}H_{12}O_2$ : C, 80.32; H, 5.40;  $OCH_3$ , 13.7. Found: C, 80.11; H, 5.23;  $OCH_3$ , 13.8.<sup>11</sup>

<sup>5</sup> Menzies method.

<sup>6</sup> Phenol was used as a solvent [Weishut, *Monatsh.*, **33**, 1165 (1912)]. In this instance, as well as when acetic anhydride was used as a solvent, the apparatus used (Gattermann-Wieland, "Die Praxis des organischen Chemikers," Walter de Gruyter, Berlin and Leipzig, 1928, p. 71) was modified to the extent that a 5-cc. dropping funnel was fused to the carbon dioxide inlet tube. The sample and phenol were placed in the apparatus and the hydriodic acid added through the dropping funnel.

<sup>7</sup> Bistrzycki and Yssel de Schepper, *Ber.*, **31**, 2792 (1898).

<sup>8</sup> Bistrzycki and Yssel de Schepper<sup>8</sup> recorded the melting point as 145–146°.

<sup>9</sup> Liebermann [*Ann.*, **212**, 25 (1882)] recorded the melting point as 302°.

<sup>10</sup> The melting point reported by Nourrisson [*Bull. soc. chim.*, [2] **46**, 206 (1886)] is 110–111°.

<sup>11</sup> Phenol was used as a solvent.



The structure of the methoxyanthrone was proved by its conversion into 2-methoxy-anthraquinone by oxidation. Eleven and two-tenths grams of the methoxyanthrone, suspended in 80 cc. of acetic acid, was treated with 11 g. of sodium dichromate, dissolved in 10 cc. of hot water. The mixture soon began to boil. After it had been heated for one hour on a steam-bath it was cooled and the crystalline reaction product recrystallized from acetic acid. Nine and seven-tenths grams of pale yellow 2-methoxyanthraquinone was obtained; m. p. 194–195°. <sup>12</sup>

When 2-hydroxyanthrone was oxidized in the manner described above, 2-hydroxy-anthraquinone was formed; m. p. 303–304°.

**2-Methoxy-9-(4'-methoxyphenyl)-anthracene (X).**—4-Methoxyphenylmagnesium iodide was prepared from 23.4 g. of 4-iodoanisole, 2.4 g. of magnesium, 45 cc. of dry benzene and 45 cc. of ether. Nine and four-tenths grams of 2-methoxyanthrone-9, suspended in 50 cc. of benzene, was added to the Grignard reagent and the mixture heated for four hours. After decomposition of the reaction mixture with ice and ammonium chloride, removal of the solvents and steam distillation, 5.2 g. of the anthracene was obtained. After recrystallization from acetic acid and then from benzene-petroleum ether (30–60°) it melted at 175–176°. The compound is very soluble in benzene, slightly soluble in ether and alcohol. The solutions all exhibit a blue fluorescence.

*Anal.* Calcd. for  $C_{22}H_{18}O_2$ : mol. wt., 314; C, 84.05; H, 5.77;  $OCH_3$ , 18.5. Found: mol. wt. (benzene), 313; C, 83.72; H, 5.63;  $OCH_3$ , 19.7. <sup>13</sup>

Because of its instability no attempt was made to isolate the primary product of the reaction, 2-methoxy-9-(4'-methoxyphenyl)-9,10-dihydroanthrol-9 (IX).

**2-Methoxy-9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10 (XI).**—Five grams of the above-mentioned anthracene, suspended in 25 cc. of acetic acid, was treated with 3.5 g. of sodium dichromate dissolved in 3 cc. of hot water. The mixture soon began to boil. After the reaction had subsided the mixture was heated on a steam-bath for five minutes, cooled and the crystalline product removed by filtration. The yield was 4.7 g. After recrystallization from acetic acid the anthrone melted at 199–201°. The material is slightly soluble in benzene and insoluble in alcohol and ether.

*Anal.* Calcd. for  $C_{22}H_{18}O_4$ : mol. wt., 346; C, 76.29; H, 5.24;  $OCH_3$ , 17.7. Found: mol. wt. (benzene), 362; C, 76.23; H, 5.24;  $OCH_3$ , 17.9. <sup>14</sup>

The anthrone was also obtained from 2-methoxyanthraquinone and 4-methoxyphenylmagnesium iodide. To the Grignard reagent prepared from 5.8 g. of 4-iodoanisole, 0.6 g. of magnesium and 15 cc. of ether there was added 4.7 g. of 2-methoxyanthraquinone, dissolved in 100 cc. of benzene. The mixture was heated for four hours, decomposed and the reaction product subjected to steam distillation. The gummy residue was dissolved in 10 cc. of hot acetic acid. The solution was allowed to cool, whereupon 1.4 g. of unchanged methoxyanthraquinone separated. This was removed immediately by filtration. After some time 2.3 g. of 2-methoxy-9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10 precipitated from the filtrate. After several recrystallizations from acetic acid the compound melted at 199–200°. The mixed melting point with the substance obtained by oxidation of 2-methoxy-9-(4'-methoxyphenyl)-anthracene was 199–201°.

**2-Methoxy-9,9-di-(4'-methoxyphenyl)-anthrone-10 (XV).**—The ethyl ester of 2-(4'-methoxybenzyl)-benzoic acid (XII) was prepared from the methoxybenzylbenzoic

<sup>12</sup> Graebe and Bernhart [*Ann.*, **349**, 222 (1906)] reported the melting point to be 186.5° while Kauffler [*Ber.*, **37**, 65 (1904)] reported 195–196°.

<sup>13</sup> Acetic anhydride was used as a solvent [Herzig, *Monatsh.*, **9**, 544 (1888)].

<sup>14</sup> Acetic anhydride was used as a solvent.

acid, alcohol and hydrogen chloride. The ester boiled at 214–216° under approximately 10 mm. pressure. Twenty-seven grams of the ester, dissolved in 80 cc. of ether, was added in small portions to the Grignard reagent obtained from 93.6 g. of 4-iodoanisole, 9.6 g. of magnesium and 200 cc. of ether. After the mixture had been heated for four hours, it was decomposed with ice and ammonium chloride. A crystalline by-product, insoluble in the ether layer,<sup>15</sup> was removed by filtration. The ether layer was subjected to steam distillation for some time and the oily product, 2-(4'-methoxybenzyl)-4'',4'''-dimethoxytriphenylcarbinol (XIII), converted into 2-methoxy-9,9-di-(4-methoxyphenyl)-9,10-dihydroanthracene (XIV) in the following manner. The carbinol was dissolved in 150 cc. of acetic acid which had been partially saturated with hydrogen chloride. The deep red solution was heated for two hours on a steam-bath. Most of the solvent was removed from the solution, which had now become brown in color, and the residue was poured into water. The gummy anthracene (XIV), which we could not obtain in solid form, was oxidized to the anthrone. The anthracene, dissolved in 180 cc. of acetic acid, was heated for four hours with 24 g. of sodium dichromate dissolved in 12 cc. of hot water. The greater part of the acetic acid was removed and water was added to the residue. The solid product obtained was recrystallized several times from acetic acid. The yield of the anthrone was 12 g.; m. p. 183–184°.

*Anal.* Calcd. for  $C_{29}H_{24}O_4$ : C, 79.78; H, 5.54;  $OCH_3$ , 21.0. Found: C, 79.66; H, 5.38;  $OCH_3$ , 21.3.<sup>16</sup>

**2-Methoxy-9,9,10-tri-(4'-methoxyphenyl)-9,10-dihydroanthrol-10 (XVI).**—To 4-methoxyphenylmagnesium iodide, prepared from 4.7 g. of 4-iodoanisole, 0.48 g. of magnesium and 15 cc. of ether, there was added 2.18 g. of 2-methoxy-9,9-di-(4'-methoxyphenyl)-anthrone-10 suspended in 50 cc. of benzene. The mixture was heated for four hours, decomposed and the ether-benzene layer subjected to steam distillation. The gummy product, which soon became solid, was recrystallized from alcohol and then from acetic acid; m. p. 193–194°.

*Anal.* Calcd. for  $C_{36}H_{32}O_5$ : C, 79.37; H, 5.93. Found: C, 78.78; H, 5.86.

### Summary

The preparation of the following compounds has been described: 9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10, 2-hydroxyanthraquinone, 2-methoxyanthrone-9, 2-methoxy-9-(4'-methoxyphenyl)-anthracene, 2-methoxy-9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10, 2-methoxy-9,9-di-(4'-methoxyphenyl)-anthrone-10, 2-methoxy-9,9,10-tri-(4'-methoxyphenyl)-9,10-dihydroanthrol-10.

<sup>15</sup> Barnett, Cook and Nixon [*J. Chem. Soc.*, 505 (1927)] obtained a by-product, insoluble in ether, from the interaction of phenylmagnesium bromide and ethyl 2-benzylbenzoate and suggested that the compound might be a pinacol.

<sup>16</sup> Acetic anhydride was used as a solvent.









